HIV, HCV, HBV, Microbial Translocation and Liver Cancer
Tamar Taddei, MD
Associate Professor of Medicine
Yale Section of Digestive Diseases
Epidemiology of Liver Cancer

- Hepatocellular carcinoma (HCC) is rising in incidence globally; tripled in the US in over the last three decades
- Chronic liver disease (HBV/HCV/ALD/NASH) is a prerequisite
- HCC is the leading cause of death in cirrhosis
- 5th most common cancer in men worldwide, 2nd leading cause of cancer death globally (841,080 new cases and 781,631 deaths in 2018)

Ryerson AB et al. *Cancer* 2016
Bray F et al. *Cancer* 2018
Bray F et al. *CA Cancer J Clin* 2018
HCV Infection Accounts for the Rise in HCC

- Latency from infection to cirrhosis is variable
- Governed by lifestyle, comorbidities, etc.
HCC in the US “Birth Cohort”

- Born before 1945 (aged > 55 years at death)
- Born 1945-1965 (aged 35-68 years at death)
- Born 1966-1970 (aged 35-47 years at death)

Deaths per 100,000 persons

Death Year

Liver cancer is a major cause of morbidity and mortality among HIV+
- Age is increasing
- HCV coinfection common
- Alcohol use common
- After HIV-1 RNA suppression, weight gain common

Accounting for these risk factors, HIV also influences course of HCC
- HIV+ have excess risk
- Preliminary data suggest more HCC events occur without cirrhosis
Hepatocarcinogenesis is Complex

- Paradoxical anti-oncogenic effects of classical oncoproteins
- Multiple pathways at play without dominance of a single driver mutation

Tsai W-L and Chung RT. Oncogene 2010
Feng GS. Cancer Cell 2012
Complexity Leads to Heterogeneity of HCC Growth Pattern and Morphology Variants
Innate lymphoid cells
Treg cells
TLR Signaling
Modulation of inflammation

Mucus production
Epithelial repair and renewal
Tight junction assembly
Antimicrobial peptide synthesis

Microbial diversity, competition
Control of pathogen expansion
Short chain fatty acid production

Wardill HR et al. *EBioMedicine* 2019
HIV Leads to *Irreversible* Gut Damage

- HIV infection
  - Viral replication
  - Chronic inflammation
  - Loss of IL-17 (Th17/Tc17)
- Damages the GI tract
- Induces translocation
- Remains perturbed despite cART

Mudd JC and Brenchley JM. *J Infect Dis* 2016
Microbial Translocation

- Microbial translocation: a consequence of disruption of the intestinal barrier integrity
- Associated with a range of states/diseases
  - intestinal ischemia
  - inflammatory bowel disease
  - graft-versus-host disease
  - chronic viral infections HIV and HCV
  - alcohol use
  - cirrhosis
- Microbial translocation products are a driving force of systemic immune activation

Lattanzi B et al. *Aliment Pharmacol Ther* 2018
HCV Leads to *Reversible* Translocation

- Surrogate markers of microbial translocation (sCD14, LBP) higher in untreated HCV+ patients than healthy subjects; early studies suggest they *normalize* after DAA
- I-FABP, a marker of enterocyte damage is not altered by HCV infection, suggesting epithelial damage is unlikely
The Senescence Associated Secretory Pathway

- HIV/HCV coinfected accumulate senescent cells in their livers owing to impaired CD4 T-cell function; this is not observed in patients with HCV infection only.

Kang TW et al. Nature 2011
The Gut-Liver Axis and Fibrosis → HCC

- Liver and intestine communicate via the biliary tract, portal vein and systemic mediators
- Liver primarily influences gut microbiota composition and gut barrier integrity
- Gut regulates bile acid synthesis, glucose and lipid metabolism in the liver
- Pro-inflammatory changes in the liver and intestine mediate fibrogenesis, cirrhosis and HCC
- Alcoholic and nonalcoholic fatty liver diseases share key characteristics, such as dysbiosis, permeability, bile acid shifts and ethanol and choline metabolites.
- Etiology of liver disease may affect the microbiome
- Microbiome-based, diagnostic, prognostic and therapeutic modalities for liver diseases/HCC are in our future

Tripathy A et al. *Nat Rev Gastroenterol Hepatol* 2018
Understanding the Gut/Liver Axis in HIV

Tripathy A et al. Nat Rev Gastroenterol Hepatol 2018
HIV & Aging Mechanisms for Hepatocellular Cancer

Comparing HIV+ and uninfected, determine if:
• Cumulative exposure to hepatotoxic medications (including ART) differentially increase risk of HCC or alter its histology.
• Obesity or diabetes differentially increase risk of HCC or alter HCC histology.

Among HIV+ on ART, determine if:
• Cumulative exposure to immune activation and dysfunction and HIV-1 RNA increase risk of HCC or alter its histology.
Future Directions

• Determine the contribution of tissue resident memory T cell dysfunction to the elevated incidence of HCC in persons living with HIV
  – Aim 1: Characterize peripheral and tissue resident T cell compartments in HIV+ and HIV- patients with and without HCC
  – Aim 2: Analyze T cell receptor (TCR) clonality and diversity in the cancer microenvironment
  – Aim 3: Determine whether changes in liver tissue $T_{RM}$ cells during the transition from inflammation and fibrosis to HCC in a mouse model mimic those seen in HCC in PLWH.
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